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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,978	11/15/2006	Martin Pruschy	4-32911A	3436

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ONE HEALTH PLAZA 104/3
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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,978	PRUSCHY, MARTIN	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/6/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/6/07 is acknowledged and has been reviewed.

Status of Claims

Claims 1-10 (this should recite claims 1-8, 10 and 11 are pending). Claims 4-9 are amended.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Applicant is required to correctly renumber the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 8 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 provides for the use of compound of formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "compound of formula I" in the claim. There is insufficient antecedent basis for this limitation in the claim. The compound formula referred to is not in the claim.

Also, the use of parenthesis does not clearly convey whether the part in parenthesis is part of the claimed composition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims1-8 and 11 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a proliferative diseases such as prostate, glioma and thyroid as specified in the specification (page 2) with ionizing radiation, does not reasonably provide enablement for treating of a wide variation of proliferative disease in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.
Nature of the invention.

The claims are directed to treating a proliferative disease with compound of formula I in combination with ionization radiation.
The disease and tumor are not specific and thus encompass the treatment of cancer or tumor in general.

State of the prior art.

While the state of the art is relatively high with regard to the treatment of specific cancer types, the state of the art with regard to treating cancer broadly is underdeveloped. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against all cancer types. The Cecil reference (cited by Examiner) clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective for each and every type of cancer (see page Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Level of ordinary skill in the art.

The level of ordinary skill in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular anticancer agent or in combination with thereof that is effective against a very wide variation of proliferative diseases.

Level of predictability in the art.

The lack of significant guidance from the present specification or prior art with regard to the actual treatment of all cancers or tumors in a patient with the claimed active ingredients makes practicing the claimed invention unpredictable.

Breadth of claims.

The complex nature of the subject matter to which the present claim is directed is exacerbated by the breadth of the claim. The claim is extremely broad due to the vast

number of possible cancer types represented by the term "a proliferative disease" or "tumor".

Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification does not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with this claim. Applicants have failed to provide guidance and information to allow the skilled artisan to ascertain that the present active agents are effective against all types of cancers or tumors. The limited enablement does not support all cancers or tumors as are being claimed.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for epithilone derivatives of formula I, does not reasonably provide enablement for prodrug ester thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

the quantity of experimentation necessary

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

the presence or absence of working examples

There is no direction in the specification concerning produgs; there are no working examples for a prodrug of a compound of formula I.

The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body., e) Wolff

(Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue; the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) Banker, G.S. Et al, "Modem Pharmaceutics, 3ed." Marcel Dekker, New York, 1996, page 596. The first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

The breadth of the claims includes numerous of the hundreds of thousands of compounds of formula.

Undue experimentation will be required to determine if any particular epithilone derivatives is, in fact, a prodrug. The first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compound. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

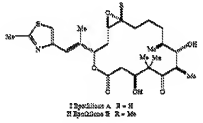
A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Vite et al. US 6,605,599.

The claims are drawn to a method of treating a proliferative disease in a subject in need of such administration an epothilone derivative of formula I with an ionization agent.

With regard to the instant claims 1- 3 and 7, the reference discloses an



epothilone wherein A is O, R is hydrogen or lower alkyl and Z is O in a pharmaceutically acceptable salt in combination with radiation see col. 1, lines 14-30 and col. 6, line 20. Please note that both forms epothilone A and B are disclosed therein. The reference further teaches the compounds of formula I is administered to humans with variety of proliferative diseases see col. 5, lines 23-67.

Administering the drug in combination with an ionization agent to therapeutically affect against the disease proliferation is considered as anticipatory as required by instant claims 4-5.

Delaying of progression of a proliferative disease is an inherent property of the compound of formula I combined with ionization radiation as required by instant claims 6 and 8.

The reference further discloses tumors such as breast, kidney, ovary known as solid proliferative tumors, thus the said limitation of claim 9 is met.

Claim 11 is rejected under 35 U.S.C. 102(e) as being anticipated by Bandyopadhay et al WO 02/058699.

The reference discloses the compounds of epothilone A and B see page 1, lines 21-24 are placed in a kit see page 6. It is considered that instruction of how to use it, is within the kit and thus anticipatory.

In the instant case, the kit claims are drawn to an old article or composition, which further comprises labeling instructions. The intended use, which is recited on the label or package of the insert, lacks a function relationship because the insert or label does not physically or chemically affect the chemical nature within the article of manufacture, and furthermore, the old article or old composition of the kit can still be used by the skilled artisan for other purposes. Therefore the old article or composition which are comprised with the claimed kit are unpatentable over the prior art, because they function equally effectively with or without the labeling, and accordingly no functional relationship exists between the instructions for use and the composition.

Thus the claims are addressed as being drawn to an article of manufacture comprising an old composition contained in a kit and a package insert, the instructions

on the insert bearing no patentable weight with regard to double patenting, 102 and 103 rejections.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/S. V. G./
Examiner, Art Unit 1618

10/3/08